Title

Differing risk factor profiles of ischemic stroke subtypes: evidence for a distinct lacunar arteriopathy?

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Title

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Running title

Risk factors of ischemic stroke subtypes

Tables and figures

2 figures

2 online tables, 1 online figure

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Background and Purpose Differences in risk factor profiles between lacunar and other ischemic stroke subtypes may provide evidence for a distinct lacunar arteriopathy, but existing studies have limitations. We overcame these by pooling individual data on 2875 patients with first-ever ischemic stroke from five collaborating prospective stroke registers that used similar, unbiased methods to define risk factors and classify stroke subtypes.

Methods We compared risk factors between lacunar and non-lacunar ischemic strokes, altering the comparison groups in sensitivity analyses, and incorporated these data into a meta-analysis of published studies.

Results Unadjusted and adjusted analyses gave similar results. We found a lower prevalence of cardioembolic source (adjusted OR: 0.33, 95% CI 0.24 to 0.46), ipsilateral carotid stenosis (OR: 0.21, 95% CI 0.14 to 0.30), and ischemic heart disease (IHD) (OR 0.75, 95% CI 0.58 to 0.97) in lacunar compared with non-lacunar patients, but no difference for hypertension, diabetes, or any other risk factor studied. Results were robust to sensitivity analyses and largely confirmed in our meta-analysis.

Conclusions Hypertension and diabetes appear equally common in lacunar and non-lacunar ischemic stroke, but lacunar stroke is less likely to be caused by embolism from the heart or proximal arteries, and the lower prevalence of IHD in lacunar stroke provides further support for a non-atherosclerotic arteriopathy causing many lacunar ischemic strokes. Our findings have implications for how clinicians classify ischemic stroke subtypes, and highlight the need for further research into the specific causes of and treatments for lacunar stroke.

About one quarter of ischemic strokes are caused by lacunar infarcts,[1] resulting from the occlusion or, perhaps, leakiness[2] of one of the small perforating arteries supplying the deep subcortical areas of the brain. The arterial pathology remains poorly understood, with proposed mechanisms including lipohyalinosis, arteriosclerosis, poor cerebral blood flow, vasospasm, or abnormal endothelial function.[3] Much of our current understanding is based on the clinicopathological studies of Miller Fisher and colleagues in the 1960s and 70s. Progress since then has been limited, but there is growing evidence to suggest that the lacunar arteriopathy may differ from the atherothromboembolic processes that lead to occlusion of large intra- and extracranial arteries, causing most other ischemic strokes.[2-4]

One indirect approach to better understanding the arterial pathology of lacunar ischemic stroke is to look for differences in the vascular risk factor profiles of lacunar versus non-lacunar ischemic stroke, which may reflect distinct underlying pathologies and causes. In a previous meta-analysis of published studies that used an unbiased method (independent of vascular risk factors) to classify ischemic stroke subtypes, we found no difference in the prevalence of most risk factors.[5] In particular, contrary to the widespread view that hypertension and diabetes are more common in lacunar ischaemic stroke,[6] we found no excess of diabetes, and only a slight excess of hypertension, but we did find a lower prevalence of atrial fibrillation and carotid stenosis in patients with lacunar ischemic stroke. However, we could not adjust for the potential confounding effects of age, sex and other vascular risk factors, the definitions both of risk factors and of the non-lacunar comparison group varied between studies, and data on several risk factors of potential interest were sparse.

We overcame these shortcomings in the present study by pooling individual patient data from five prospective stroke registers that used identical, unbiased methods of classifying ischemic stroke subtypes and consistent risk factor definitions. We compared risk factors for lacunar versus non-lacunar ischemic stroke, assessing the effects of adjusting for potential confounders and varying the comparison groups in pre-defined sensitivity analyses. We also updated our previous meta-analyses, incorporating data from our stroke register pooling project.

Methods

We obtained data from stroke registers that had not necessarily (indeed most had not) already published on risk factor-ischaemic stroke subtype associations but were able to provide data for inclusion in pooled individual patient data analyses. These were two phases of our hospital-based stroke register in Edinburgh,[7,8] and three community-based stroke registers in Perth, Australia, and in Lund and Orebro in Sweden, all of which recruited from predominantly Caucasian populations.[9-11] Each register had the required ethical approvals. In each, a stroke physician had assessed patients as soon as possible after the stroke, prospectively recording demographic and clinical details, including vascular risk factors and results of brain imaging and other investigations. Definitions of risk factors are given in the footnotes to Online Table 1.

We included all patients with a clinically evident stroke, demonstrated to be ischemic by the absence of recent intracerebral hemorrhage on appropriately timed computed tomography (CT) or magnetic resonance (MR) brain imaging, or at autopsy. We assigned ischemic stroke subtypes according to the presumed site and size of the causative infarct (anterior circulation lacunar or cortical [including striatocapsular] infarction, or posterior circulation infarction) using the clinical features of the stroke

(Oxfordshire Community Stroke Project syndromes),[12] modified if necessary by the findings on brain imaging (or at autopsy) if an infarct considered relevant to the presenting stroke was present. We excluded patients whose subtype was either undetermined or known to be due to a specific unusual cause such as arterial dissection.

Statistical analyses

We analysed data with STATA version 8.

In the primary analysis we included all patients with a first-ever-in-a-lifetime anterior circulation ischemic stroke, excluding cases of posterior circulation stroke, among which lacunar and non-lacunar ischemic strokes are often difficult to distinguish reliably. We determined the crude association between each risk factor and ischemic stroke subtype, by calculating register-specific and Mantel-Haenszel fixed-effect pooled odds ratios (ORs), using I^2 to assess heterogeneity between registers.[13] We used Student's t-test to compare mean ages.

We used logistic regression to obtain ORs adjusted for age, sex, and register, and, in a second model, also adjusted for hypertension, diabetes, and any other risk factors that differed significantly between lacunar and non-lacunar groups in unadjusted analyses.

We estimated extent of misclassification of ischemic stroke subtypes by calculating the proportion of patients with a visible relevant infarct on their brain scan whose final classification placed them in a different comparison group from that based on the clinical syndrome alone. We applied this proportion to the patients with no visible relevant infarct to estimate the extent of residual misclassification.

We also calculated ORs as described above in five pre-defined sensitivity analyses: (1) including patients with recurrent as well as first-ever events; (2) excluding those with a potential cardioembolic source; (3) including posterior circulation ischemic strokes in the non-lacunar comparison group; (4) comparing small versus large vessel disease ischemic strokes, using a modified Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification[14] (online Figure); and (5) among patients with a visible relevant infarct only, to assess the effects of excluding all potentially misclassified patients.

Updated meta-analysis

We updated our previous meta-analysis of published studies comparing risk factors in lacunar versus non-lacunar ischemic strokes, following the same rigorous methods (details published previously[5]). We pooled unadjusted data from the primary analysis of our collaborative stroke register project with data extracted from all other studies published by June 2008 that had used a similar method for classifying ischemic stroke subtypes. We used Cochrane Review Manager[15] to determine study-specific and Mantel-Haenszel fixed-effect pooled ORs, assessing heterogeneity between studies using I^2.[13]

Results

The five registers contributed data on a total of 5101 patients with stroke, of whom 2875 had a first-ever-in-a-lifetime anterior circulation ischemic stroke (1062 lacunar, 1813 non-lacunar).

Mean age ranged from 67 to 76 years. Patients in the hospital-based registers were younger than in the community-based ones, and lacunar cases were younger than non-lacunar (mean 68 versus 71 years, $p < 0.001$). There were approximately equal

numbers of men and women in the non-lacunar group, but slightly more men (58%) in the lacunar group ($p < 0.001$). The proportion of lacunar cases (32 to 42% of first-ever anterior circulation ischemic strokes) was similar in the different registers. All registers provided data on hypertension, diabetes, ischemic heart disease, and smoking. Data were not available from all registers for the remaining risk factors (Online Table 1).

For each risk factor, unadjusted ORs were generally very similar across all registers, with no significant between-register heterogeneity. Unadjusted and adjusted analyses generally yielded very similar results (Figure 1). Cardioembolic source and carotid stenosis were much less common in lacunar than non-lacunar ischemic stroke, while hypertension and diabetes did not differ between subtypes. A history of ischemic heart disease was less common in lacunar ischemic stroke, and remained so in the fully adjusted analyses (OR lacunar versus non-lacunar: 0.75, 95% CI 0.58 to 0.97). Although both smoking and excess alcohol consumption appeared commoner in lacunar versus non-lacunar ischemic stroke, these associations did not persist following multivariable adjustment.

343 of 1806 patients in the primary analysis with a visible relevant infarct on their brain scan were allocated to a different comparison group (and so correctly reclassified) than would have been the case based on their clinical syndrome alone. Applying this proportion to the 1069 patients with no visible relevant infarct gave an estimated 203 patients residually misclassified out of 2875 in the primary analysis population (7%), with similar proportions misclassified in each comparison group.

For each of the five planned sensitivity analyses, results were generally very similar to those from the primary analyses (Online Table 2).

Updated meta-analysis

Previously we identified 10 published studies that had used a risk factor-independent clinical syndrome and imaging-based method of classifying ischemic stroke subtypes.[16-25] One overlapped with the Lund register in our pooled stroke register analysis and was therefore excluded from our updated meta-analysis.[18] We found three further relevant studies [26-28] one of which superseded an earlier study.[28]

Figure 2 shows the ORs for lacunar versus non-lacunar ischemic stroke from our previous meta-analysis, from the unadjusted primary analyses of our collaborative stroke register project, and from our updated meta-analysis including our collaborative data and newly identified published data. These three estimates were generally very similar for all risk factors. The most consistent findings were a lower frequency among patients with lacunar ischemic stroke of ischemic heart disease (updated meta-analysis OR: 0.76, 95% CI 0.68 to 0.85), cardioembolic source (OR: 0.40, 95% CI 0.35 to 0.46); and carotid stenosis (OR for ipsilateral stenosis: 0.23, 95% CI 0.19 to 0.29; for contralateral stenosis: 0.29, 95% CI 0.21 to 0.41); and no difference between subtypes for diabetes or prior TIA. The updated meta-analysis showed a slight excess of hypertension among patients with lacunar ischemic stroke (OR 1.12, 95% CI 1.02 to 1.24). It also suggested that smoking and excess alcohol consumption were more common in lacunar ischemic stroke, but these results may be subject to residual confounding since these associations disappeared in our fully adjusted individual patient data analyses. There was moderate heterogeneity between studies in our updated meta-analysis for each of IHD, cardioembolic source, ipsilateral stenosis, previous TIA and smoking.

Discussion

Analyses of our large collaborative stroke register dataset revealed important differences in the risk factor profiles among patients with lacunar compared with non-lacunar ischemic stroke. There was a striking similarity between unadjusted and adjusted results and robustness to a series of sensitivity analyses for most risk factors, justifying our updated meta-analysis of unadjusted results from published studies. The individual patient data results were largely confirmed by the updated meta-analysis, and suggest that many fewer lacunar than non-lacunar ischemic strokes are caused by emboli from the heart or proximal arteries. Furthermore, the lower prevalence of atherosclerosis in not only carotid but also coronary arteries among lacunar cases shows that these patients are less likely to have atherosclerosis in other vascular territories. Thus, a distinct non-atherosclerotic arteriopathy may cause many lacunar ischemic strokes.

There are a number of strengths to our study. First, our pooled analyses benefited from methodological similarities between the included registers; large numbers of patients; and adjustment for potential confounding factors. Second, the inclusion of our individual patient data in the updated meta-analyses almost doubles the existing published data on hypertension and diabetes from studies using risk factor-independent methods of classifying ischemic stroke subtypes, and more than doubles the existing data for many other risk factors. Third, a series of sensitivity analyses in which we varied the comparison groups did not materially alter the results.

Our study has some potential weaknesses. First, the distribution of ischemic stroke subtypes and risk factors may differ between hospitalised and non-hospitalised patients.[29] Our hospital-based register patients were, however, recruited from both

hospital admissions *and* outpatient clinics, making them more representative. Furthermore, accurate classification of pathological types and subtypes of stroke requires early specialist clinical assessment, appropriately timed brain imaging and other investigations, essentially confining analyses from community-based stroke registers to those patients having hospital-based assessment. Second, although a clinical syndrome and brain imaging-based method of classification is probably the least biased method to use when investigating risk factor-stroke subtype associations, there will still be some misclassification of stroke subtypes.[30] Since the estimated proportion of misclassified patients (7%) in the two compared groups of patients was similar, misclassification may have diluted any true risk factor – ischemic subtype associations. It is, however, reassuring that our analyses confined to patients with a visible relevant infarct on brain imaging produced similar results to the primary analysis. Third, there may have been some misclassification of risk factors, since in our stroke registers we ascertained exposure to risk factors retrospectively. Misclassification of risk factor status is likely to have occurred to a similar extent in both comparison groups, and so may have diluted estimates of association. Thus we may have failed to detect some risk factor-subtype associations, but there are no robust prospective data to check this. The level of detail required for adequate distinction between ischemic stroke subtypes has rarely been available in prospective studies with detailed assessment of risk factors at baseline,[31,32] and the limited amount of subtype information available is based on potentially biased risk factor-dependent or purely imaging-based classification methods.[33,34] Finally, we were unable to assess the relationship between raised cholesterol and ischemic stroke subtypes, since data on pre-stroke cholesterol levels

were not available. Current evidence suggests no definite association between cholesterol level and ischemic stroke.subtype.[5,35]

An earlier meta-analysis of four population-based studies found risk factor-stroke subtype associations broadly similar to our own, but did not assess ischemic heart disease. Hypertension was more frequent in lacunar compared with non-lacunar ischemic stroke, but this result could be attributed to a single large study that used strict application of the TOAST criteria with their reliance on risk factors (including hypertension) to define subtypes.[29]

In a recently published study that compared risk factors in patients with presumed small versus large vessel disease (using a modified TOAST classification similar to ours, excluding hypertension and diabetes from the risk factor definitions), hypertension appeared much more common in patients with small vessel disease.[36] However, the comparison groups were not recruited consecutively or contemporaneously, and the definition of hypertension included raised blood pressure post-stroke. Our study found no excess of hypertension in patients with small versus large vessel disease.

Our findings have important implications for both clinicians and researchers. We consistently found no evidence for the still widely held belief that hypertension and diabetes are more prevalent in lacunar than non-lacunar ischemic stroke. Thus clinicians should not be guided by the presence or absence of these risk factors when assigning an etiological stroke subtype. Our data suggest that few lacunar ischemic strokes are caused by emboli from the heart or proximal arteries, and our newly established finding of a lower prevalence of previous ischemic heart disease in lacunar versus non-lacunar cases suggests that the former are less prone to atherosclerosis in other vascular territories, providing further indirect evidence for a

distinct non-atherosclerotic arteriopathy underlying many lacunar strokes. However, since patients with lacunar stroke can have any of the aforementioned risk factors, they should still be investigated for all of these.

Further clinical, pathological and imaging-based studies are needed to unravel the nature of the vascular pathology underlying lacunar ischemic stroke, to enable the development of specific approaches to the acute treatment and prevention of this common stroke subtype. However, this study adds to an increasing body of evidence for a distinct arteriopathy of lacunar stroke, including differences in the retinal microvasculature and in the leakiness of the blood brain barrier.[2,37,38] In addition, since the most appropriate therapeutic interventions for different ischemic subtypes may differ, future trials of treatments for acute stroke and long term secondary prevention after stroke (including, for example, trials of thrombolytic and antithrombotic drugs) should accurately distinguish ischemic stroke subtypes and ideally have sufficient statistical power to detect differences between subtypes in the effects of the treatments being assessed.

Figure legends

Figure 1. Unadjusted, age and sex-adjusted, and fully adjusted odds ratios for each risk factor (lacunar versus non-lacunar ischemic stroke).

Open diamonds: Mantel-Haenszel pooled ORs, stratified by register; grey diamonds: age, sex and register-adjusted pooled ORs; black diamonds: fully adjusted ORs;.N: total number of lacunar or non-lacunar patients; n: number of lacunar or non-lacunar patients with each risk factor; OR: odds ratio; CI: confidence interval.

*Heterogeneity between studies in the unadjusted analysis.

Figure 2. Unadjusted odds ratios for each risk factor (lacunar versus non-lacunar ischemic stroke) in the previous and updated meta-analysis.

Open diamonds: ORs obtained in previous meta-analysis; grey diamonds: ORs obtained in unadjusted individual patient data analysis; black diamonds: ORs obtained in updated meta-analysis (including the individual patient data).

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